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JUSTICIRESINOL, A NEW FURANOID LIGNAN FROM *JUSTICIA GLAUCA*[1]

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ABSTRACT.—Justiciresinol, a new lignan isolated from *Justicia glauca*, has been characterized as 2-(4-hydroxy-3-methoxyphenyl)-4-[(4-hydroxy-3,5-dimethoxyphenyl)methyl]-tetrahydrofuran-3-methanol [**1**], based on spectroscopic data and chemical transformations.

In continuation of our phytochemical studies on *Justicia* plants (1–3), we have reinvestigated *Justicia glauca* Rottl. (Acanthaceae). The residue from the aqueous 95% EtOH extract of the whole plant was fractionated with petroleum ether, EtOAc, and MeOH. The EtOAc fraction, on chromatography over Si gel, yielded five known lignans, (+)-pinoresinol (4), (+)-medioresinol (3), (+)-lariciresinol (3), (+)-isolariciresinol (1,3), and (+)-8-methoxyisolariciresinol (3), a new lignan, named justiciresinol [**1**], and sitosterol-3-*O*-glucoside (3). The known compounds were identified by comparison of spectral data and mmp's with authentic samples.

Justiciresinol [**1**] was obtained from petroleum ether/EtOAc as colorless crystals: mp 127°, $[\alpha]_D$ +21.95° in $CHCl_3$, analyzed for $C_{21}H_{26}O_7$ (*m/z* 390 $[M]^+$). Its ir spectrum showed bands at 3530 and 1610 cm^{-1}, suggestive of hydroxyls and aromatic rings, respectively. It formed a triacetate **2**, $C_{27}H_{32}O_{10}$, with pyridine and Ac_2O under normal conditions. A study of its uv, ir, and ^{1}H-nmr data in comparison with those of lariciresinol reveal that justiciresinol [**1**] is a lariciresinol type of lignan containing an additional methoxyl on one of the aromatic rings. The eims of **1** exhibited prominent peaks at *m/z* 167 [**a**] and 151 [**b**] suggesting that the additional methoxyl could be present on the benzyl moiety at C-4. It may be noted that an isomeric lignan **3**, isolated from *Wikstroemia elliptica*, in which the methoxyl was present at C-5′, exhibited an intense mass fragment at *m/z* 181 [**c**] (5). Further, the placement of the additional methoxyl in justiciresinol [**1**] at C-5″ is supported by the two-proton singlet observed at δ 6.42 in the ^{1}H nmr and identical carbon chemical shifts observed for C-2″ and C-6″, C-3″ and C-5″. The stereochemistry of justiciresinol [**1**] could be assigned as that of lariciresinol, based on comparison of their ^{1}H-nmr signal patterns (H-2, -3, -4, and -5) and magnitude and sign of optical rotations.

Final confirmation of the structure of justiciresinol [**1**] was obtained by its isomerization into (+)-8-methoxyisolariciresinol (3) with HCl in MeOH. Thus, the structure of justiciresinol could be formulated as 2-(4-hydroxy-3-methoxyphenyl)-4-[(4-hydroxy-3,5-dimethoxyphenyl)methyl]-tetrahydrofuran-3-methanol [**1**] and its triacetate as **2**.

It is significant to note that lariciresinol, which is a major lignan in *J. glauca*, is a cytotoxic substance (5) as well as insect antifeedant (6). Justiciresinol showed low cytotoxicity (adriamycin, the anticancer drug, served as

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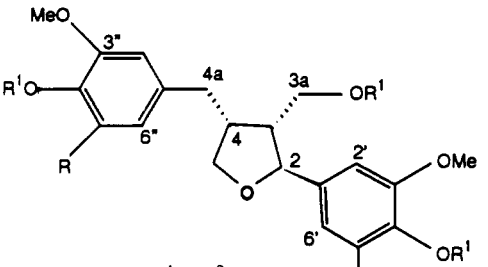

1 R = OMe, $R^1 = R^2 = H$
2 R = OMe, R^1 = Ac, $R^2 = H$
3 $R = R^1 = H$, R^2 = OMe

$Ar^2—CH_2^+$ (**a**) $Ar^1—CO^+$ (**b**) $Ar^2—CO^+$ (**c**)

Ar^1 = 4-hydroxy-3-methoxyphenyl
Ar^2 = 4-hydroxy-3,5-dimethoxyphenyl

a positive control) against three human tumor cell lines, A-549 (human lung carcinoma, ED_{50} 31.3 μg/ml), MCF-7 (human breast carcinoma, ED_{50} 22.3 μg/ml), and HT-29 (human colon adenocarcinoma, ED_{50} 18.3 μg/ml) (7).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mp's were determined on a Mel-Temp apparatus and are uncorrected. The uv spectra were recorded on a Shimadzu UV-240 spectrophotometer, ir spectra on a Perkin-Elmer 983 spectrometer, ^{1}H-nmr spectra on a Bruker AM 500 MHz NMR spectrometer in $CDCl_3$ using TMS as internal standard operating at 500.135 MHz, and ^{13}C-nmr spectra on a Bruker AM 500 MHz NMR spectrometer operating at 125.759 MHz. Eims were recorded on Kratos MS 25 mass spectrometer, and optical rotations were measured on a Jasco DIP-360 digital polarimeter. Cytotoxicity tests were made at the Cell Culture Laboratory, Purdue Cancer Center, using standard protocols.

PLANT MATERIAL.—The plant material (whole plant) was collected from the Sri Venkateswara University Campus, Tirupati, during October and November 1987 and authenticated by Research and Specimen Cell, PID, CSIR, New Delhi. The voucher specimen is on deposit at the Department of Botany, S.V. University, Tirupati, India.

EXTRACTION AND FRACTIONATION.—The shade-dried milled plant material (ca. 3.5 kg) was extracted with aqueous EtOH (95%). After removal of the solvent, the dark green gummy residue (ca. 150 g) was fractionated with petroleum ether (60–80°), EtOAc, and MeOH. The solvent was removed from the EtOAc extract under vacuum, and the gummy residue (ca. 50 g) was chromatographed over Si gel (ACME, 100–200 mesh) and eluted with mixtures of C_6H_6/EtOAc in increasing polarity. Seven compounds were isolated and further purified by rechromatography over Si gel and recrystallization.

IDENTIFICATION OF KNOWN COMPOUNDS.—(+)-*Pinoresinol*.—(+)-Pinoresinol (0.14 g) was obtained as colorless crystals from petroleum ether/EtOAc: mp 113–114°; $[\alpha]_D$ +113.93° (c = 0.31, $CHCl_3$) [lit. (4) +51° (c = 0.1, $CHCl_3$)]. Spectral data were consistent with the literature values (4), and identity was established by direct comparison with (+)-pinoresinol kindly provided by Dr. T. Deyama (4).

(+)-*Medioresinol*.—(+)-Medioresinol (0.5 g) appeared as pale brown flakes from MeOH: mp 179–180° [lit. (3) 178–179°], $[\alpha]_D$ +58.09° (c = 0.21, $CHCl_3$).

(+)-*Lariciresinol*.—(+)-Lariciresinol (7.0 g) was obtained as colorless needles from EtOAc: mp 170–172° [lit. (3) 170–172°]; $[\alpha]_D$ +19.20° (c = 0.76, Me_2CO).

(+)-*Isolariciresinol*.—(+)-Isolariciresinol (0.8 g) was obtained as colorless globules from C_6H_6/MeOH: mp 159–160° [lit. (1,3) 159–160°]; $[\alpha]_D$ +70.50° (c = 0.49, Me_2CO).

(+)-*8-Methoxyisolariciresinol*.—(+)-8-Methoxyisolariciresinol (0.5 g) was obtained as colorless crystals from C_6H_6/MeOH, mp 160–162° [lit. (3) 160–162°]; $[\alpha]_D$ +61.7° (c = 0.66, Me_2CO).

Sitosterol-3-O-glucoside.—Sitosterol-3-*O*-glucoside (0.2 g) was obtained as a colorless solid from MeOH, mp 288–290° [lit. (3) 288–290°]. It formed a tetraacetate with pyridine/Ac_2O, mp 161°.

(+)-*Justicresinol* [**1**].—Compound **1** (0.04 g):

colorless crystals from petroleum ether/EtOAc: mp 127°, $[\alpha]_D$ +21.95° (c = 0.22, $CHCl_3$); uv (MeOH) λ max 207.0, 228.5, 281 nm; ir (KBr) ν max 3530, 1610 cm^{-1}; ^1H nmr (500 MHz, $CDCl_3$) δ 2.42 (1H, m, H-3), 2.53 (1H, dd, J = 13.5, 11.1), 2.93 (1H, dd, J = 13.5, 4.9, H-4a), 2.73 (1H, m, H-4), 3.70–3.95 (2H, m, H-3a), 3.77 (1H, dd, J = 8.6, 5.9), 4.04 (1H, dd, J = 8.6, 6.5, H-5), 4.77 (1H, d, J = 6.7, H-2), 6.42 (2H, s, H-2″ and H-6″), 6.80 (1H, dd, J = 8.1, 1.8, H-6′), 6.87 (1H, d, J = 1.8, H-2′), 6.87 (1H, d, J = 8.1, H-5′), 3.87 (6H, s), 3.88 (3H, s, -OMe^s), 1.67, 5.45, and 5.65 (1H each, OH^s); ^{13}C nmr (125 MHz, $CDCl_3$) δ 82.7 (C-2), 52.7 (C-3), 60.9 (C-3a), 42.5 (C-4), 33.8 (C-4a), 72.8 (C-5), 134.7 (C-1′), 108.3 (C-2′), 146.7 (C-3′), 145.1 (C-4′), 114.2 (C-5′), 118.8 (C-6′), 131.5 (C-1″), 105.3 (C-2″ and C-6″), 147.1 (C-3″ and C-5″), 133.0 (C-4″), 55.9 and 56.3 (-OMe^s); eims m/z $[M]^+$ 390 (100%), 360 (5.4), 205 (13.4), 194 (24.7), 168 (43.5), 167 (52.3), 153 (22.3), 151 (31.3), 137 (30.6).

ACETYLATION OF JUSTICIRESINOL.—Justiciresinol (10 mg) was treated with Ac_2O-pyridine (1:1) (1 ml) at room temperature overnight. Usual workup of the reaction mixture gave the triacetate **2** (10 mg) as a colorless syrupy liquid: uv (MeOH) λ max 207.0, 274.5 nm; ir (KBr) ν max 1760, 1730, 1600, 1495 cm^{-1}; ^1H nmr (500 MHz, $CDCl_3$) δ 2.04 (3H, s, -OAc), 2.31 (3H, s, -OAc), 2.33 (3H, s, -OAc), 2.58 (2H, m), 2.73 (1H, m), 2.85 (1H, m), 3.80 (6H, s), 3.84 (3H, s), 4.11 (1H, m), 4.22 (1H, m), 4.40 (1H, m), 4.87 (1H, d, J = 5.7), 6.41 (2H, s), 6.87 (1H, dd, J = 8.1, 1.8), 6.96 (1H, d, J = 1.8), 7.00 (1H, d, J = 8.1); ^{13}C nmr (125 MHz, $CDCl_3$) δ 82.8 (C-2), 49.0 (C-3), 62.6 (C-3a), 42.1 (C-4), 34.1 (C-4a), 72.7 (C-5), 141.5 (C-1′), 109.6 (C-2′), 151.0 (C-3′), 138.9 (C-4′), 122.6 (C-5′), 117.6 (C-6′), 138.4 (C-1″), 105.1 (C-2″ and C-6″), 152.1 (C-3″ and C-5″), 127.1 (C-4″), 168.8, 169.1 and 170.9 (-OAc^s), 55.9 and 56.1 (-OMe^s), 20.4, 20.6, and 20.8 (-OAc^s).

ISOMERIZATION OF JUSTICIRESINOL.—To justiciresinol [**1**] (10 mg) in MeOH (1 ml) was added a drop of concentrated HCl, and the reaction mixture was heated on a steam bath for 1 h. Solvent was removed under vacuum, and the residue was crystallized from EtOAc. The product obtained, mp 160–162°, $[\alpha]_D$ +61.7° (c = 0.66, Me_2CO), was found to be (+)-8-methoxyisolariciresinol described above, mmp 160–162°.

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LITERATURE CITED

1. C.B. Rao, K. Suseela, P.V. Subba Rao, P.G. Krishna, and G.V. Subbaraju, *Indian J. Chem.*, **23B**, 787 (1984).
2. G.V. Subbaraju, K.K.K. Kumar, B.L. Raju, and K.R. Pillai, in: "Abstracts." 17th IUPAC International Symposium on the Chemistry of Natural Products, New Delhi, 1990, p. 165.
3. G.V. Subbaraju and K.R. Pillai, *Indian J. Chem.*, **28B**, 558 (1989).
4. T. Deyama, T. Ikawa, S. Kitagawa, and S. Nishibe, *Chem. Pharm. Bull.*, **35**, 1785 (1987).
5. C. Duh, C.H. Phobee Jr., J.M. Pezzuto, A.D. Kinghorn, and N.R. Farnsworth, *J. Nat. Prod.*, **49**, 706 (1986).
6. K.C. Chitra, P.V.R. Reddy, G.V. Subbaraju, and K.R. Pillai, in: "Abstracts." 17th IUPAC International Symposium on the Chemistry of Natural Products, New Delhi, India, 1990, p. 85.
7. Y.-H. Hui, J.K. Rupprecht, J.E. Anderson, K.V. Wood, and J.L. McLaughlin, *Phytother. Res.*, **5**, 124 (1991), and references cited therein.

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